University of North Carolina-Chapel Hill
Consent to Participate in a Research Study
Adult Subjects
Biomedical Form

IRB Study # 99-EPA-283
Consent Form Version Date: March 20, 2006
Title of Study: Physiological, Cellular, and Biochemical Effects of Diesel Exhaust in Healthy Young Adults

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What are some general things you should know about research studies?
You are being asked to take part in a research study. To join the study is voluntary. You may refuse to join, or you may withdraw your consent to be in the study, for any reason.

Research studies are designed to obtain new knowledge that may help other people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Deciding not to be in the study or leaving the study before it is done will not affect your relationship with the researcher, your health care provider, or the University of North Carolina-Chapel Hill. If you are a patient with an illness, you do not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study. You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?
The main purpose of this research study is to determine if a component of outdoors air pollution, diesel exhaust, causes inflammation in the lungs. Results from this study may increase the understanding of how gaseous and particulate air pollutants (which causes the haze seen in some polluted cities) may adversely affect the functioning of human lungs. This understanding may be especially important for patients with asthma or other cardiopulmonary diseases.

 Initials_____

Are there any reasons you should not be in this study?

You should not participate in this study if…

1. You have a history of lung disease and/or active allergy including: hay fever, dust allergies, rhinitis, asthma, chronic bronchitis, chronic obstructive pulmonary disease, tuberculosis, coughing up blood, recurrent pneumonia, chronic or allergic rhinitis or acute or chronic sinusitis.
2. You are unable to participate in moderate exercise
3. You are a diabetic
4. You have a history of bleeding or coagulation disorders
5. You have a history of chronic exposure to dusts or chemical fumes
6. You are allergic to lidocaine or other local anesthetics used in dental procedures
7. You have a history of cardiovascular disease
8. You have high blood pressure
9. You are pregnant
10. You are arthritic or take regular doses of NSAIDs (aspirin-like medications, ibuprofen), or acetominophen, or corticosteroids.
11. You cannot remain in the local area for 24 hours after the bronchoscopy
12. You are currently breast feeding

How many people will take part in this study?

If you decide to be in this study, you will be one of approximately ten (10) people in this research study.

How long will your part in this study last?

Your participation in this study will last for one training session (today) **for about 2-3 hours,** and two exposure sessions, each exposure session consisting of about 6-7 hours on the first day and about 3-5 hr on the next day, for a total of 5 days. Therefore your participation may take up to approximately 27 hours. The interval between the first 2 day session and the second 2 day session will be a minimum of 3 weeks.

Storage of some of the samples from you in this study may be up indefinitely.

What will happen if you take part in the study?

During the course of this study, the following will occur:

A. General Description of the Project:

Ten normal healthy subjects (males or females) between the ages of 18 and 40 will be recruited and complete the study.. Female subjects cannot be pregnant and participate in this study. Prior to each exposure, urine testing and menstrual history will be obtained to rule out pregnancy. Screening examinations will take place at the EPA.

Today you will have a training session at the EPA for about 2-3 hours to familiarize yourself with some of the techniques you will perform. These include instruction on the use of the stationary bicycle to be used during the study, and how to perform spirometry and an exhaled breath collection. After satisfactorily completing the training session, you will be ready for the

Initials_____

exposure, and an appointment date will be set up for you through a U.S. EPA contracting company (currently Westat). A list of medications, environmental exposures, exercise restrictions, and foods to avoid for the exposure and follow up days will be given to you at this time. You are to avoid fumes and smokey rooms in addition to not smoking. You should not eat pan fried or grilled meat before midnight of the exposure day.

DAY 1:

BEFORE EXPOSURE:

On Day 1 of exposure, you will be exposed in a random order to either filtered air or diesel exhaust diluted approximately 1:30 with filtered air to achieve an approximate diesel exhaust particle (DEP) concentration of 100 $\mu g/m^3$ for 2 hr. [Random order is akin to flipping a coin; it means you an equal chance of receiving filtered air or diesel exhaust on your first exposure based on the chance selection by an engineer (who is not part of the research team). As the engineer is the only one to know what your exposure is, you and the research team will be "blinded" or in the dark as to what exposure type you receive. This particle concentration is representative of DEP levels which you would inhale if you were occupationally exposed to DEP, such as being a truck driver, but less than sites in some mines that utilize diesel-generated power. You would also be exposed to a similar total amount over about 10 hr at a busy intersection in a polluted city (such as Los Angeles) where DEP concentrations have been measured at 22 $\mu g/m^3$.

Before the exposure, nurses will also attach several electrocardiograph (ECG) leads to your chest. It may be necessary to clean and shave the areas of your chest where these leads will be placed. Excessive deodorant, skin lotions, and body sprays may interfere with the function of some of these leads so we will ask you to not apply these to your chest area on the days you report to the HSF. The leads will be connected to 2 monitors (small recording devices about the size and weight of a portable tape player) to obtain readings of your heart rate and rhythm. One of these heart monitors will be removed when you leave for the day. The other monitor, a portable electrocardiograph (ECG) monitor, will remain connected to you until you return the next day. You will be asked to recline quietly and breathe at a constant rate for 20 minutes, after which the ECG monitor will take a 10-minute measurement of your heart rhythm. It is important that you do not fall asleep during this 30-minute period.

You will be asked to fill out a symptom questionnaire before the exposure. Additionally, other baseline procedures will be performed, including a blood draw, urine collection, exhaled breath collected over about 15-30 min, and lung function determined by spirometry and airways resistance by plethesmography.

Following the baseline procedures, you will have attached on the outside of your clothes two small personal monitoring devices which captures some of the particles and gases in the exposure chamber for later chemical analyses. The purpose of wearing these samplers is to measure pollutant levels and to determine how well the monitors work in terms of measuring the pollutants so that it may possibly be used for nonchamber studies.

DURING EXPOSURE:

You will enter the exposure chamber for 2 hr. You will exercise moderately for one-half the exposure time in 15 min exercise then 15 min rest intervals. You will be allowed to eat your lunch if you have brought it, and drink water supplied by the EPA during the exposure period.

AFTER EXPOSURE:

Initials_____

After the exposure, some procedures will be performed, including a blood draw, exhaled breath collection, spirometry, plesthesmography, urine collection, determination of heart rate variability, and filling out a symptom questionnaire. The ECG will be worn by you overnight to monitor your cardiac activity. After a checkout in the medical station, you will be discharged from the facility. You will be given a phone number and pager number for the physician on duty. Should any untoward symptoms occur before returning the next morning, you can call the physician for an evaluation.

DAY 2:

You will return to the Human Studies Facility the following day (Day 2). You will be checked in at the medical station. You will fill out a follow-up symptom questionnaire. At that time, a blood draw, exhaled breath collection, spirometry, plethesmography, and urine collection will be performed. Your heart rate variability will again be determined. You will then be prepared for bronchoscopy. This will involve insertion of a flexible tube ("bronchoscope") through one side of the nose and placement into one of your airways. A portion of one of your lungs will be washed with sterile saline. In addition, a small amount of surface cells will be retrieved from one of your airways by gently scraping with a three special brushes which will sample the airway tissue (three brush biopsies. The effect of diesel exhaust on lung inflammation will be specifically determined by counting the number of inflammatory cells (neutrophils) recovered in the lung lavage (washings). Additionally, the washings themselves, breath condensate, and cells recovered by brush biopsy and forceps biopsy will be examined to see if you have been affected by diesel exhaust in such a way as to promote an increase in the number of inflammatory cells (neutrophils). This will be done by determining if there are increases in certain substances which promote inflammation or are indicative of inflammation. The washings, breath, blood, and cells may be examined for other biochemical mediators which are present during inflammatory responses, indicate altered immune function, suggest altered blood clotting parameters, and/or provide an estimate of the amount of diesel exhaust that is deposited in the body. Your urine will be analyzed for an estimate of how much diesel exhaust deposited in your body. The specimens (cells and fluid) may be stored for as-yet-undesignated tests; genetics testing may be performed on those specimens. The effect of diesel exhaust on some aspects of lung physiology will also be assessed by spirometry and plethesmography.

After completion of the procedures on Day 2, an appointment will be made for you to return for an identical set of two day procedures for the second exposure session.

B. Detailed Description of Specific Procedures: Exposure, Bronchoscopy, and Breath Collection

If the results of the screening session today are satisfactory, you will participate in a training session. You will be informed of the design of the experiment and possible risks involved. You will be given adequate opportunity to have any questions answered and will sign the Informed Consent Form. The training session will familiarize you with spirometry and breath collection techniques.

If you agree to do the study, you will be asked to come back to two study sessions; each session will last two days with about 6-7 hours on the first day and 4-5 hours on the second day.

 Initials_____

1. Exposures to filtered air and diesel exhaust:

You will be expected at the medical station of the U.S. EPA Human Studies Facility (at 104 Mason Farm Road) at 8:00 on the morning of the exposure (Day 1). You will be asked several questions regarding your overall health and medicine usage. Use of a nonsteroidal anti-inflammatory (NSAIDs) medication (e.g., aspirin-like, ibuprofen ("Motrin", "Advil"), or acetominophen, or suprofen (Celebrex) within the last 48 hr will disallow your continuation with the study or possibly cause rescheduling of you in the study. Alcohol is not to be taken within 24 hr of the exposure. It is strongly urged that you not eat grilled or pan fried meat the day of the exposure (i.e., from after midnight to 5:00 PM of the exposure day). The investigators have the right to cancel your participation or reschedule your participation in the study if it is thought that the medication taken might alter the way the exposure affects you, or if you are not compliant with the protocol conditions. If you are a woman, you will be asked specifically about your menstrual history and will be given a urine pregnancy test once again. The results of the pregnancy test will be held in strict confidence and revealed only to you. You will only be allowed to continue in the study if your pregnancy test is negative.

To begin the exposure, you will enter an environmental chamber which consists of a small chamber (approximately 6 ft x 6 ft x 8 ft) containing exercise equipment. A glass window allows the staff to observe you in the chamber at all times. During the exposure, you will be asked to alternate exercise on a stationary bicycle (15 minutes) and then rest (15 minutes). Each exposure session will last two (2) hours.

During the exposure, you will wear several adhesive chest electrodes which will be used to monitor your heart rate and rhythm. You can terminate the exposure at any time. The staff will be monitoring your progress continuously from the control room and will stop the exposure if you experience any unexpected symptoms (e.g., dizziness, headache, chest pains). You can communicate at all times with the staff from the chamber via an intercom.

2. Bronchoscopy:

You will be expected at the medical station of the Human Studies Facility (EPA Human Studies Facility on Mason Farm Road) at 8:00 on the next morning for the bronchoscopy (Day 2). If you have had anything to drink or eat since midnight the night before the bronchoscopy, or if you have taken a nonsteroidal anti-inflammatory medication and/or alcohol during the past 24 hr, you will not be allowed to proceed. The bronchoscopy procedure is frequently used in the diagnosis of lung disease of both adult and pediatric patients. The procedure has been used safely (>1000 times) for several years in studies conducted at Human Studies Facility, The purpose of the bronchoscopy procedure is to obtain fluids and cells from the lower areas of the respiratory tract, i.e., the trachea and smaller airways and alveolar regions. These materials will be analyzed in HSD laboratories to obtain information about the role of various chemical substances and cells in the pulmonary response to particle exposure.

The bronchoscopy procedure will be performed at the HSF medical station by especially trained, experienced pulmonary physicians. The bronchoscope is a highly flexible fiberoptic tube two feet long and about 0.5 centimeter in diameter (about the thickness of a pencil). It is an optical device with a light at the end which can be used to transmit images to a camera connected at the other end. Using the bronchoscope, the physician can see into your airways and direct the placement of the bronchoscope. A small channel allows fluid to pass through the bronchoscope and is used to insert a very small brush into the airway to retrieve surface cells.

Initials_____

Before you undergo bronchoscopy, an intravenous catheter will be placed in a vein in your arm to possibly give you medication (atropine) before the procedure starts (a saline lock is a needle that stays in your arm for a short time). The lock will remain in place so that it can be used to give you drugs in case there are any problems during the procedure. You will also have adhesive recording electrodes placed on your chest, a blood pressure cuff on your arm and an oximeter (a small clothespin like device) adhered on your finger tip to allow the medical staff to monitor your blood pressure, heart rate and blood oxygen levels during the procedure. No sedatives and/or narcotics are administered during bronchoscopy.

Before proceeding, the nurse will again make certain that you have had nothing to eat or drink since midnight the previous night. She will then give you a lidocaine solution and ask you to gargle with it for a few seconds in order to anesthetize your throat. You will then be asked to inhale (snort) a small amount of lidocaine jelly through one nostril to anesthetize your nose and the back of your throat. A Q-tip with lidocaine jelly will be gently inserted into your nose to ensure that your nose is completely numb before the bronchoscope is inserted. The procedure will not begin until your nose and throat are well anesthetized. If this cannot be accomplished, the bronchoscopy will not be performed. A tube delivering oxygen will be placed *inside* your other nostril. This is done as a precaution during all bronchoscopies carried out at the HSD.

To start the procedure, the physician will pass the bronchoscope through your anesthetized nostril into the back of your throat and to a point above your vocal cords. He will then inject a lidocaine solution to numb your vocal cords before passing the bronchoscope into your trachea. More lidocaine, up to what is considered a safe maximum dose for a healthy adult, is injected at various points in your trachea and airways to minimize coughing during the procedure. You may experience some cough during the procedure. This is a normal reflex caused by the presence of the bronchoscope in your airway.

The bronchoscope will then be gently wedged in an airway in the right lung and sterile saline will be injected into your lung through a channel in the bronchoscope. The saline will then be gently suctioned from your lung through the bronchoscope. This sequence will constitute one wash. A total of six (6) washes will be performed in the same lung area, with the first wash being about 20 cc saline and the remaining washes being approximately 50 cc. A total of about 270 cc (about one-half pint) of sterile saline will be used during the bronchoscopy procedure. Approximately 75 % of the saline injected into your lungs can be recovered by aspiration through the bronchoscope. The remaining 25 % or so (*about* 75 cc) is expected to remain in your lungs. The saline left in your lungs should not cause you any difficulty breathing or harm you in any way, and will be completely absorbed by your lungs within 48 hours. After the lavage is performed, brush biopsies of your airway surface epithelial cells will be taken. In brush biopsies, a very small brush (3 millimeters in diameter) will be inserted through the channel in the bronchoscope. The brush is visible to the physician performing the procedure through the bronchoscope. Small amounts of surface cells are scraped from the airway by gently brushing the airway several times. Three (3) brush biopsies are taken at one site in the left lung. The total time the bronchoscope will be in your airways will be up to 20 to 35 minutes. You can terminate the bronchoscopy at any time, and still receive payment for the procedure.

After the procedure, the oxygen cannula will be removed if your oxygen saturation is acceptable. Similarly, the chest electrodes will be removed if your heart rhythm is normal. Vital signs will be monitored every 30 minutes for the first hour and hourly thereafter. During this time you will sit in a recliner at the medical station for an observation period of ninety (90) min. You will not have any food or drink during this time.

Initials_____

After the recovery period, the nurses will check your gag reflex. The gag reflex normally prevents you from inhaling food or liquids into your airway. Since this reflex will be anesthetized during the procedure, you will be prevented from eating or drinking until the anesthesia wears off. This normally takes about one to one-and-one-half hours. Once your gag reflex returns, you will be given some juice to sip and a snack.

A physician will check you after the recovery period. You will be discharged if your vital signs and chest examination are normal. Before leaving you will be given the phone number of the medical station (966-6232) and pager number and home telephone number of the physician who performed the bronchoscopy or the physician on call with instructions to call if you experience any adverse symptoms, such as: 1) Persistent fever or fever above 101 ^{o}F, 2) Persistent cough, 3) Sputum (phlegm) production, 4) Chest pain, 5) Coughing up any amount of blood, 6) Nose bleeds, 7) Shortness of breath, 8) Wheezing, 9) Hoarseness or sore throat, 10) Dizziness. You will need to remain in the local area for 24 hours after the end of the bronchoscopy.

3. Collection of exhaled (expired) breath :

Exhaled breath is collected three times each session: On Day 1, once before and after exposure, and on Day 2 just prior to bronchoscopy. These breath collections assist in identifying the presence of inflammation in the lung, and estimating how much diesel exhaust deposited in your lungs.

One procedure involves collection of breath condensate. At normal breathing frequency and volume, you will breathe air in through your nose and exhale your breath out through your mouth into a wide plastic tubing submerged in ice water. A collection period of up to 15 minutes will be used and generally yield about 2-3 cc of fluid. You will also fill up an approximately 30 L plastic bag with exhaled breath, again breathing in through your nose and out through your mouth at normal frequency and volume. It is estimated this will take less than 5 min. Another procedure involves collection of lung gas that requires you to exhale slowly from a deep inspiration into a small bag (about 1 L) for about 20-30 sec. at a steady flow rate against some resistance. A separate procedure will require you to have a rubber stopper with tubing attached through it inserted in one nostril. You will be asked to inhale deeply and close the soft palate (as demonstrated during the training session) and a measurement will be taken within approximately 30 sec. This is repeated three times.

4. Blood

Blood will be drawn by standard techniques three times during Day 1 and 2: once before the exposure, once soon after the exposure, and once the morning of the bronchoscopy. About 80 cc will be taken per collection.

What are the possible benefits from being in this study?

Research is designed to benefit society by gaining new knowledge. The benefits to you of participating in this study may be that you may learn that you are particularly sensitive to one of the components of particulate air pollution, and this knowledge may be useful in deciding where you may live and what employment (such as working in a heavy industry job) you choose. Society in general may benefit as more is learned about how air pollution irritates the airway and injures lungs.

Initials_____

What are the possible risks or discomforts involved with being in this study?

This study might involve the following risks and/or discomforts to you:

In most people, diesel exhaust will have an unpleasant odor, and cause eye and nasal irritation. Some subjects experience headache, dizziness, and nausea, though these symptoms usually occur at higher concentrations. The amount of diesel exhaust, expressed as the particle mass concentration, to be employed in this study (i.e., approximately 100 $\mu g/m^3$) is thought to be equivalent to that encountered over several hours at a busy street in Los Angeles, and probably less in terms of amount than would be breathed during a 24 hour period in Los Angeles. Overall, it appears that at the low diesel exhaust particle concentration to be given one time for the exposure in this study, the risk of cancer, if it exists at all, is extremely low and certainly no more than what one would experience if one were to visit for a few days a particulate-polluted city in the US such as Los Angeles or New York City. This concentration is less than that used in previous controlled exposure studies of exercising young healthy human adult volunteers exposed to diesel exhaust (i.e., about 300 $\mu g/m^3$ for 1 hr). Diesel exhaust particles contain polycyclic aromatic hydrocarbons, which in high enough concentrations and repeated exposures may be carcinogens. However, the estimated particle dose in this protocol, even assuming that all inhaled particles are deposited (which is highly unlikely) is less than a total of 0.6 mg (or 600 µg) given previously in other experiments involving human nasal instillation of DEP. Your exposure to diesel exhaust may change your response to a subsequent exposure to allergens.

Carbon monoxide levels will be kept under 10 ppm, a concentration frequently exceeded in heavily trafficked cities. For comparison, values in California average 10-40 ppm. At these levels in normal healthy subjects no overt health effects are observed.

You will be exposed to aldehydes in the diesel exhaust, including formaldehyde and acetaldehyde which are carcinogenic in (nonhuman) animal studies with repeated exposures at high concentrations.

1. Particle Exposure

Exposure to air pollution particles can cause **cough, shortness of breath, chest discomfort and headache**. These symptoms typically last no more than a few hours, but could last longer if you are especially sensitive. There is a chance that exposure to particles can increase the likelihood that you will be more likely to come down with a respiratory infection within several days of the exposure. Diesel exhaust, even when diluted in this study, may have an unpleasant odor. Exposure to the air pollution particle concentrations used in this study for short periods of time have never been found to cause permanent health effects.

You will be monitored continuously during the exposure session through a window in the chamber or by closed-circuit television, and can communicate with a staff member via an intercom. Your heart rate and rhythm will also be constantly monitored for any adverse changes brought about by the exposure or the exercise. A licensed physician is always on the premises during exposures, and is available to respond to a call within 30 seconds

Some studies have shown that long term (months to years) exposure to air pollution can be associated with increased incidence of lung cancers. These results have been variable in many different studies. In no case would the risk involved in this study exceed the chance of getting cancer by spending a day in Los Angeles, New York, or any urban center where the mass of air pollution particles exceeds that used in this study.

Initials_____

2. *Telemetry and Heart Rhythm Monitoring*

There is little risk associated with monitoring your heart by ECG or blood oxygen by pulse oximetry. However, preparing your skin for placement of ECG electrodes and removing the electrodes the next day may cause some **irritation, itching, or burning** in some people. If this occurs you should call the nursing staff.

3. Bronchoscopy, Lavage, Brush Biopsy

As with all medical procedures, there are risks associated with bronchoscopy. However, experience has shown that these risks are extremely small in young, healthy subjects such as yourself. The risks associated with bronchoscopy are described in detail below.

A primary risk of bronchoscopic procedures is **discomfort to the nose and throat** brought about by the insertion of the bronchoscope through the nasopharynx. This discomfort should be alleviated or eliminated by the use of local anesthetics such as lidocaine. For this reason, you will be asked to gargle with a lidocaine solution and have lidocaine jelly placed in your nose prior to beginning the procedure. The effectiveness of the anesthesia will be tested by the nurse or physician using a cotton swab gently inserted into your nose before inserting the bronchoscope. If you experience pain or discomfort during insertion of the bronchoscope, more lidocaine will be used, up to a safe maximum amount. If adequate anesthesia cannot be achieved using this amount of lidocaine, the procedure will not take place.

A second risk of bronchoscopy is **coughing** that results from the irritation of the airway caused by the presence of the bronchoscope in the airway. Coughing is a normal reflex the function of which is to expel foreign substances from the airways. Because coughing in itself can cause mild trauma and discomfort to the airways and vocal cords, lidocaine liquid is sprayed on the airways at various sites to suppress the cough reflex. This strategy is usually not completely successful and it is expected that you will have some cough during the procedure, especially during the time of insertion of the bronchoscope into the airway. If coughing is not controllable with the lidocaine or causes you discomfort, the procedure will be terminated immediately.

On very rare occasions, bronchoscopy can induce an **asthma-like attack**. The symptoms include: chest tightness or shortness of breath as muscles in the airways spasm. This complication is extremely rare in healthy, young individuals such as yourself, who have no history of lung disease. However, should an asthma attack occur, the physician will terminate the procedure immediately, and administer asthma medication to stop the spasm of the airways. This is all that should be required to alleviate the symptoms. In the very unlikely event that you require additional treatment because the asthma attack continues, you will be transported by ambulance to the emergency room of the UNC Hospitals, located 1/4 mile away.

Nose bleeds are another risk of bronchoscopy. This is caused by trauma to the nose during the bronchoscopic procedure. Almost always, the bleeding is minor and is noticed as a few drops of blood in mucus secretions in the nostril. This bleeding usually stops on its own, without any treatment within an hour after the bronchoscopy. On very rare occasions, if the bleeding becomes moderate to severe, your nostril will be packed with sterile gauze to absorb the blood and put pressure on the site of bleeding. Should you require additional treatment, you will be transported to the UNC Hospitals Emergency Room. Major nose bleeds during bronchoscopy are extremely rare and limited to people with kidney disease or blood clotting disorders. It could also be caused by chronic use of aspirin, ibuprofen or similar drugs. You will not be allowed to participate in this study if you are presently on any medication or regularly take aspirin. Therefore, the probability of getting a major nose bleed is very small.

Initials_____

Major bleeding of the airways is another very rare (less than 1 percent) complication of bronchoscopic procedures. The chances of serious bleeding occurring in young, healthy people are even more remote. People who suffer from kidney disease, blood clotting disorders or are chronic users of aspirin-like drugs are at increased risk of bleeding during bronchoscopy. In addition, people with lung cancer or serious infections are more likely to suffer from airway bleeding during the procedure. Your medical history, the physical examination, your blood analysis and chest X-ray would reveal conditions that put you at risk of bleeding during bronchoscopy. You will not be allowed to participate in this study if you have any of these conditions. Therefore, your chances of having a serious bleeding during bronchoscopy are extremely small. Nevertheless, if you do experience bleeding during bronchoscopy, you will be under the care of an experienced physician who will take steps to stop the bleeding immediately. A special cart with emergency supplies is available to handle medical emergencies. In the event of a major bleeding episode, you will be immediately transported to the Emergency Room of the UNC Hospitals.

Pneumothorax or collapsed lung is another possible complication of bronchoscopic procedures. This condition is more likely to occur during tissue biopsy in the lung periphery, not the major central airways which will be the focus of this study. The symptoms of pneumothorax include chest pain and shortness of breath. If you experience these symptoms, you should immediately contact the medical station (966-6232), or page the physician who performed the bronchoscopy or the on-call physician. The vast majority of pneumothoraces occur within 24-48 hours of the procedure being completed. While a serious condition, a pneumothorax can be treated readily in an emergency room setting.

The lidocaine used to anesthetize your nasopharynx and control your cough can pose certain risks as well. A small fraction of the lidocaine applied to your nose and airways will be absorbed into your bloodstream, where it could cause adverse effects. Your risk of suffering side effects from the lidocaine are normally very small, but can be much greater and potentially life-threatening if you are allergic to lidocaine or other topical anesthetics. You will not be allowed to participate in this study if you have any known alleries to lidocaine or similar medications.

When used at high doses, lidocaine can also cause central nervous system effects such as **confusion, lightheadedness, itching, tremors, euphoria, or seizures.** Heart rate disturbances are also possible if too much lidocaine is used. Therefore, no more than a maximum of approximately 360 mg of lidocaine will be used. These amounts are set as the maximum safe doses recommended by the manufacturer of the drug. Should any problems arise due to the use of lidocaine, a physician will be available to treat them.

Prior to the start of the bronchoscopy, atropine may be given through a vein in your arm in order to counteract any changes in blood pressure that result from the placement of the bronchoscope into your airway and to limit the amount of secretions in your nose and throat. Atropine can cause a an increased heart rate and decreased blood pressure, dry mouth and nose for 30-60 minutes after the procedure is completed. The effects should wear off on their own soon after that.

A **low-grade fever** (less than 101 °F) occurs in a small percentage (about 25 %) of hospitalized subjects undergoing bronchoscopy and lavage. Our experience here at the EPA facility reveals <1% patients with fever after bronchoscopy. The fever is benign and responds well to Motrin or Tylenol, it should resolve completely within 24 hours. If you experience a fever greater than 101 °F or lasting longer than 24 hours, you could have pneumonia and should contact the Medical Station staff immediately, so that you can be examined and treated.

Initials_____

Pneumonia occurs in less than 1 percent of the patients undergoing bronchoscopy and BAL. Signs of pneumonia include: fever greater than 101 °F or persisting for more than 24 hours, 2) Persistent cough with or without sputum production, 3) Chest pain, 4) Shortness of breath at rest, 5) Coughing up blood. You should contact the Medical Station to be seen by a physician if you have any of these or other symptoms. As a routine precaution, the Medical Station staff will contact you between 24 and 48 hours after the bronchoscopy to inquire about any symptoms you may be experiencing.

4. Venipuncture

Placing an IV catheter in your arm carries some small risks as well. The needle stick can be momentarily **painful**, and **can leave a bruise in your arm**. The nursing staff members who will be placing the catheter are very experienced and therefore the risk is minimal. Infection is also a very small risk involved in the placement of the catheter. Again, the nurses are very experienced in the use of sterile techniques to prevent infection. On rare occasion, you may faint. If you notice redness or swelling in the area surrounding the catheter site, you should contact the medical staff at 966-6232 for treatment.

Pregnancy excludes a subject from participating in this study. Pregnancy is determined by a test of your urine, and the cost of the test is paid for by the EPA. If you are a woman and you are planning to get pregnant, you should not be in the study. Please notify the Medical Station (919-966-6232) or other listed investigators if you become pregnant during the study.

5. Personal monitors

Wearing a personal sampling device poses no expected or foreseen risk.

6. General Risks

In addition, there may be uncommon or previously unrecognized risks that might occur. You should report any problems to the researchers.

What if we learn about new findings or information during the study?

You will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

How will your privacy be protected?

No subjects will be identified in any report or publication about this study. **Data will be not be identified by your name.** Personal identifiers will be available only to the immediate research team. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-CH and EPA will take all steps allowable by law to protect the privacy of personal information. Short term storage of your files (containing your name) may be kept in the Medical Station or with the Principal Investigator, Co-Investigators, and assisting staff on the day/week of the study. Long term files storage (containing your name) are kept in the Medical Station records room, which is locked and accessible only to the Medical Station staff. The EPA Facility is accessible only to employees working in the building or to their guests and contractors given clearance through

Initials_____

employees; a guard/receptionist in the lobby will monitor all visitor entry. No highly sensitive information will be collected from you. In some cases, your information in this research study could be reviewed by representatives of the University, the research sponsor (US EPA), or some government agencies for such purposes such as quality control or safety.

What will happen if you are injured by this research?

All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury from being in this study. If such problems occur, the researchers will help you get medical care, but any costs for the medical care will be billed to you and/or your insurance company.

Neither the University of North Carolina at Chapel Hill nor the U.S. EPA has set aside funds to pay you for any such reactions or injuries, or for the related medical care. If you believe you have suffered a research-related injury, you have the right to pursue legal remedy if you believe that your injury justifies such action. The Federal Tort Claims Act, 28 U.S.C. S 2671 et seq., provides for money damages against the United States when property loss or personal injury results from the negligent or wrongful act or omission of any employee of the EPA while acting within the scope of his or her employment. Signing this consent form does not waive any of your legal rights or release the investigator, the sponsor, the institution, or its agents from liability for negligence. If a research-related injury occurs, you should contact the Director of the EPA NHEERL Human Research Protocol Office at 919-966-6217.

What if you want to stop before your part in the study is complete?

Your participation is voluntary. You may refuse to participate, or may discontinue your participation at any time without penalty, or jeopardizing your continuing medical care at this institution, or losing benefits you would otherwise be entitled to.

Dr. Madden, Dr. Devlin, Dr. Prah, or Dr. Ghio has the right to stop your participation in the study at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

Will you receive anything for being in this study?

You will be receiving up to approximately $1996 for taking part in this study. This reimbursement schedule is described below:

Subject Compensation for Procedures during Diesel Exposure Study (99-EPA-283)

PreTraining	
Recruitment Office Visit	$15
Physical Examination	$15
Bronchoscopy Physical Examination	$20
Training Day (assume 3 hr @$12/hr)	$36

First Exposure:

Day 1

 Initials_____

Hourly payment (assume 7 hr @$12/hr)	$84
Symptom questionnaire (twice @ $5 ea)	$10
Blood Draw (twice @ $25 ea)	$50
Urine Sample (twice @ $10 ea)	$20
Expired Breath Gas (3 types @ $5 each, twice)	$30
Expired Breath Condensate (twice @ $15 ea)	$30
24 hr Holter Monitoring	$100
Spirometry (twice @ $20 ea)	$40
Airways Resistance (twice @ $20 ea)	$40
Lunch	$5
Day 2	
Hourly payment (assume 4 hr @$12/hr)	$48
Symptom questionnaire (once @ $5 ea)	$5
Blood Draw (once @ $25 ea)	$25
Urine Sample (once @ $10 ea)	$10
Expired Breath Gas (3 types @ $5 each, once)	$15
Expired Breath Condensate (once @ $15 ea)	$15
Spirometry (once @ $20 ea)	$20
Airways Resistance (once @ $20 ea)	$20
Bronchoscopy	$325
Brush Biopsy (3 brushes, 6 passes)	$38
[Total payment First Exposure	$930]
Second Exposure	
Day 1 + Day 2 (same procedures as First Exposure)	$930
Completion Bonus	$50
APPROXIMATE TOTAL	**$1996**

Additionally you may be reimbursed for other possible costs, which can include extra blood sticks, extra hours spent in the study, and reasonable travel expenses from out of town. Parking will be paid by the US EPA. Money received by participants in research studies is normally treated as ordinary income by taxing authorities and we will report payments made to you to the Internal Revenue Service as required by law.

NOTE: **You should understand that your participation is voluntary. You may terminate your participation in the study at any time without penalty. If you voluntarily elect to withdraw from the study at any time or you fail to maintain compliance with eligibility requirements, you will be paid for that portion of the study that has been completed.** In the event a scheduled study activity must be cancelled by the investigators with less than 72 hours prior notice, you will be paid $12 per hour for the time scheduled and canceled, and 50% of the reimbursement amount for procedures that are canceled up to a total maximum of $100 for all procedures. You will be paid in full for any procedures that may have been started during the current visit. Cancellations could occur due to adverse weather conditions, equipment failure, and other unforeseen events. When feasible, canceled visit(s) will be rescheduled. The

 Initials_____

investigators also have the right to stop your participation in the study at any time. This could be because you have had an unexpected reaction, or because the entire study has been stopped, or for some other reason. If you are dismissed by the investigators prior to completion, you will be paid for the entire study excluding the completion bonus except in the case where you are dismissed from the study due to your failure to follow instructions.

Will it cost you anything to be in this study?
The costs of this research will be paid by the sponsor. There will be no costs to you for participating,

If you enroll in this study, you will have some tests and procedures that are only part of the research study. These procedures include blood draws, urine and breath collections, lung testing, bronchoscopy, and cardiac monitoring. All costs are paid for by the sponsor.

What if you are a UNC student?
You may choose not to be in the study or to stop being in the study before it is over at any time. This will not affect your class standing or grades at UNC-Chapel Hill. You will not be offered or receive any special consideration if you take part in this research.

What if you are a UNC employee?
Taking part in this research is not a part of your University duties, and refusing will not affect your job. You will not be offered or receive any special job-related consideration if you take part in this research.

Who is sponsoring this study?
This research is funded by the U.S. Environmental Protection Agency. This means that the research team is being compensated by the sponsor for conducting the study. The researchers do not, however, hold a direct financial interest in the sponsor.

What if you have questions about this study?
You have the right to ask, and have answered, any questions you may have about this research. If you have further questions, or if a research-related injury occurs, you should call Michael Madden, Ph.D. at 966-6257, or the EPA Medical Station at the EPA Human Studies Facility at 919-966- 6232, or the EPA NHEERL Ethics Official here at the facility at 919-966-6217.

What if you have questions about your rights as a research subject?
All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. This research has been reviewed and approved by the Committee on the Protection of the Rights of Human Subjects (Medical IRB) at the University of North Carolina at Chapel Hill. If you have any questions or concerns regarding your rights as a research subject, you may contact, anonymously if you wish, the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu. You may also contact the EPA NHEERL Ethics Official here at the facility at 919-966-6217.

 Initials_____

IRB Study #99-EPA-283 **Consent Form Version Date:** March 17, 2006
Title of Study: Physiological, Cellular, and Biochemical Effects of Diesel Exhaust in Healthy Young Adults
Principal Investigator: Michael C. Madden, PhD

Subject's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

_____ _____
Signature of Research Subject Date

_____
Printed Name of Research Subject

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Person Obtaining Consent

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